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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/929,772	08/14/2001	Robert T. Lum	96,877-W1	2293

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EXAMINER	
BERCH, MARK L	
ART UNIT	PAPER NUMBER
1624	6

DATE MAILED: 01/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/929,772	LUM ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 50-90 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 50-90 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

It should be noted that this case has a parent which is a CIP of 09/230829. The claims of this case are not entitled to the date of the parent, but only to the 2/1/99 filing date of 09/241224 because the claims here have additional material. For example:

I. R'_1 in this case can be substituted aralkyl and heteroaralkyl; not so in 09/230829.

II. The list that appears on page 74, lines 10-14 contains items not mentioned in the parent e.g. the last item on the list.

III. Claim 49, and corresponding material in the specification, did not occur in the parent.

IV. R_3 here can be alkyl of any size; not so in 09/230829.

V . Some of the claim 76 species e.g. the second one, are not seen in the parent.

Claims 50-54, 58-62, 66, 72, 79-83, 85, 87-90 rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/16452.

See Formula 1 and examples such as 1, 3, 4, 6, 7.

Claims 50-57, 60-61, 63-65, 67-71, 73-75, 79-83, 85, 87-90 are rejected under 35 U.S.C. 102(b) as being anticipated by Schow.

See species 9, 14. This is applicant's own work.

Claims 50-72, 76-83, 85, 87-90 are rejected under 35 U.S.C. 102(a) as being anticipated by 5866702.

This is the published version of a grandparent. Note that this application has 2 additional inventors, so that the reference is the work of another.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 50-57, 60-61, 63-65, 67-71, 73-75, 79-83, 85, 87-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijer.

See Table 1, species 4 and 9-16. The third proviso bars the situation where there is 6-benzylamino and 9-sopropyl, so these species are barred. However, the variant of these species with 9-methyl is obvious because such a choice appears in species 6. And the variants with 6-cyclohexylmethyl or isopentenylamino or 3-iodobenzylamino are also taught because these are species present in the table as well.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 50-90 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48-74, 76 of copending Application No. 09/929771. Although the conflicting claims are not identical, they are not patentably distinct from each other because overlapping subject matter is involved here and in the sibling case. For example, claim 55 in 09/929771 specifies R4 as 2-amino ethyl, a choice depicted in claims 68 and 73 here.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50-67, 72, 77-90 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The third proviso lacks description in the specification. The "and" in the ninth from last line of page 3 does not appear on page 78, line 7, after the first comma. There is no way of knowing whether "and" or "or" was intended missing word. For whichever choice is made, applicants must show that one of ordinary skill in the art would have known that this choice, and not the other, was intended.

Claims 81-85, 87, and 90 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The compounds are disclosed to be CDK2 inhibitors. There is no reason to think that one of ordinary skill in the art could, without undue experimentation, treat such difficult disorders with such compounds. Note the following:

A. References of cited in the parent do not support such a notion. Glab(1994) does not mention therapeutic utility. Others present use only as a possibility to be achieved by developing much better compounds. For example, Vesely (1994) says, "It is possible that, through its specificity, olomoucine may lead to a compound which will preferentially inhibit the proliferation of certain tumor cells." Olomoucine is excluded by proviso from the claims. This shows that basic research is still required to obtain the necessary selectivity. Abraham (1995) says that "olomoucine may constitute a lead

compound for the design of new anti-tumor agents." Similarly, Schultz-Gahmen (1995) referring to its results, says it "should prove useful in modifying and improving the lead compound." But, a lead compound is one which is not actually ready for use; it is by its nature something which needs to be modified by additional research.

B. Although olomoucine itself is not potent enough to be effective, the testing presented in Table 6 established that many of these compounds are either less effective as CDK2 inhibitors than olomoucine, or are not effective to actually inhibit cell proliferation even in this crude test, or both. Indeed, a number of species displayed no measurable activity in either test. The specification says that cell proliferation inhibition has an IC(50) of "preferably less than 0.5 g/ml" which is a reasonable standard, but only 4 species met that standard. Even on this very simple *in vitro* test, the results show that most compounds are ineffective.

C. Claims 83 and 85 call for the treatment of cancer in general. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different

methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

D. Further, claim 81 is even broader, covering presumably any cell proliferative disorder. A proliferative disorder is anything that causes any abnormal tissue that grows by cellular proliferation more rapidly than normal, or continues to grow after the stimulus that initiated the new growth has ceased, or shows lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, clonal proliferative disorders including the various Myelodysplastic Syndromes such as Refractory anemias, certain types of abnormal wound healings, different types of abnormal angiogenisis, pulmonary fibrosis, macular degeneration, myeloproliferative disorders such as primary polycythemia and myleofibrosis, and rheumatoid arthritis. There is no such thing that an agent which is effective against such disorders generally, since they are so diverse, nor is there any reason to think that such an agent could be made to work.

E. Further, it covers healthy processes as well, because cell proliferation is an essential process of life. The claim, in effect covers the treatment of people who are in fact perfectly healthy, and covers inhibition of the proliferation of cells essential for life.

F. The inclusion of gout in claim 83 makes no sense at all. Patients with gout are normally told to avoid high purine foods, in order to reduce uric acid secretion.

G. Lupus (SLE) and MS are among the most intractable nervous system disorders, evidence that the skill level in this art is very low relative to difficulty of task. No one has been able to treat these with CDK2 inhibitors.

H. It is noted that this application discloses an additional property which "some of the compounds of this invention" (specification, page 3) have, viz, inhibition of I B- kinase. However, it is noted that a) it is unclear which compounds actually have this property, aside from the ones tested on page 73 and b) this is one of many kinases about which relatively little is known and c) it is not asserted that any of the utilities in these rejected claims are connected to this property.

Claims 50-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 50 has a new proviso, requiring that at least one of R_4 and R_5 must be a group substituted by $NR_{20}R_{23}$. This means that the second and 4th provisos need to be removed, and the first R_3 choice in the 5th proviso needs to be removed, because these are all forbidden values of R_3, as they lack the $NR_{20}R_{23}$ substituent. In addition, the third proviso needs to be modified, because its first condition is always met.

2. In addition, some species in claim 76 violate this proviso. For example, the first species, the last page 19 species, and the species bridging line 4-5 of page 20 all have both R4 and R5 as hydroxyethyl.
3. Applicants have $NR_{20}R_{23}$ in many places and $NR^{20}R^{23}$ in many others. The same form must be used.
4. The claims state "2, 6, 9 trisubstituted" but R_2 is permitted to be H, which gives just disubstituted. Is R_2 = H in error?
5. The term "acyl" (e.g. page 3, line 4) is indefinite. Does this embrace acids of S? P? As? What does the stem look like, i.e. if the acyl is e.g. RC(O), what is R?
6. Further, this is on a list of "hydrocarbon" (see first word on that line) which is wrong, since acyl by its very nature cannot be a hydrocarbon. Was Acyl the wrong word? Likewise, other choices e.g. heterocycle and heteroaralkyl are not hydrocarbons.
7. All uses of "heteroaryl" (e.g. page 3, line 4) seem superfluous, since this is already covered by heterocyclic.
8. "Heterocyclic" is indefinite. What is the size of the ring? What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated?
9. The "each having one to 20 carbons" (e.g. page 3, line 5), makes no sense, since almost all of these must have more than one carbon. An aryl for example, must have at least 6; and aralkyl must have at least 7. Note what was correctly done at R^{22} definition.

10. It is unclear whether the claim 55 choices are permitted to be optionally substituted or not. It might be argued that claim 52's "which ... are optionally substituted" carried through to claim 55, so that this optional feature exists there as well. However, if that were true, there would have been no reason to have included both "substituted" and "unsubstituted" in claim 56, since the same reasoning would apply to claim 56's dependency on claim 55 as well. Similarly, there would be no reason to include the substituted choices in claims 58 and 59, etc. This gives the impression that without the "substituted" language, the substituted choices are not intended. Alternatively, claim 55 could be understood as saying just literally was it says, viz, just the aralkyl and heteroaralkyl, and not the substituted versions thereof. In that case, however, claim 56 would be improperly dependent on claim 55.
11. "Includes" (R_2 in Claim 61) is open-ended, and thus improper for a Markush group. Suggested is "wherein the options substituent is selected from the group consisting of". Likewise last line of page 13 and elsewhere.
12. "Amide" (e.g. page 4, line 2) is indefinite. There is no way of knowing whether applicants intend just carboxylic acid amides, or whether sulfonic, phosphonic, etc amides are intended. But even if carboxylic acid amido is intended, the term is undefined. Such a molecule generically has the formula RC(O)NR'R". One of the R choices will be used to attach, depending on whether the amido is C- or N-bound. What is the nature of the other two R groups? Can the two of them together form a ring, and if so, of what type? The term "aryl or aryl or heteroaryl" before the "amide" doesn't really answer the question. Do these terms define the

R, the R', or the R" or is it any of them? And does that mean that all the substituents must come from that list, or just that it must be present? For example, if this were understood to be carboxamide bounded via the C, i.e. -C(O)NR'R", would C(O)N(alkyl)(alkenyl) qualify? It does have the alkyl, which is on the list, but it also has the alkenyl, which is not on the list. Moreover, it should be "amido" as this is a moiety.

13. The R'_1 is not amino of the second proviso makes no sense as R'_1 could never be H in the first place.

14. In claim 81, "therapeutically effective" for what? Inhibiting cell proliferation is a biochemical process, not therapy per se, which is treatment of a disorder. Cell proliferation is not a disorder, but an essential body process.

15. The choice of "thiomethoxy" seen in e.g. third from last line of page 20 is unclear. Is methylthio (CH_3S-) intended or is mercaptomethoxy ($HSCH_2O$-)? Something else? Whatever choice is selected must be supported by the specification.

16. R_2 as cycloalkyl (e.g. claim 61) and substituted cycloalkyl (e.g. claim 72) makes the claims improperly dependent on claim 50, which does not provide for such choices. Deletion is suggested, because neither does page 5 of the specification.

17. Claims 79-80 are improperly dependent on claim 50, which makes no provision for salts.

18. What in claim 79 is a "cationic salt" -- what is the cation? Is for example a N of the purine being quaternized?

19. The "from 1" on line 1 of e.g. page 14, line 5 makes no sense. From 1 to what?

20. In claim 83, "host graft disease" is defective; presumably, "host-vs.-graft disease" is intended.

21. The R^2 of page 14, line 11 should be R^{23}.

22. A period exists in the middle of claim 50, at page 2, first line below structure.

23. The last three choices of page 2, line 5 below the formula and the first choice of line 6 are all superfluous because these are already covered by the R^{22} of line 6. This problem also occurs at third from last line of page 2 and wherever R^{22} is used as a substituent.

24. Claim 89 is unclear. If intended as a compound claim, then it is identical to claim 1, and hence is improperly dependent on claim 1. If intended as a composition claim, then it lacks a carrier.

25. Provisions for acyl being substituted e.g. page 3, line 5 make no sense, because acyl is already open-ended and could have any type of substituent to begin with.

26. A letter is missing after the 4- in the fifth from last line of claim 76.

27. A number of the claim 83 disorders are not considered a "cell proliferative disorder." Gout is a manifestation of hyperuricemia. Crystals of sodium urate cause acute inflammatory arthritis. It is not treated with antiproliferative agents, but instead with anti-inflammatory agents. Multiple Sclerosis is of unknown cause, although it is suspected of being of immunological origin. It is not characterized by cell proliferation, but is a destruction of the preformed myelin. Treatment does not involve standard antiproliferative agents, but instead involves the use of corticosteroids, and even that is for symptom relief; it does not treat the underlying disorder. Similarly, lupus (SLE is assumed) arise from

hyperactivity of the immune system. "Host graft" (presumably, "host-graft-graft disease" is intended) is not normally considered a cell proliferation disease, but is more or less an expected response to foreign lymphocytes, when the body is unable to reject them. Type I diabetes is a disorder of the carbohydrate mechanism caused by little or no endogenous insulin. Rheumatoid arthritis is generally classified as an autoimmune disorder. Restinosis is not a cell proliferation disorder, but is a generic term covering recurrent narrowing.

28. The first and third choices in claim 78 are the same. Is one of them in error?

29. The last 3 claim 78 choices do not appear in claim 77, so that claim 78 is improperly dependent on claim 77.

30. The last claim 60 term should have 20 as a superscript, not a subscript.

31. The last phrase in claim 90 is unclear. Derived from how? It is noted that most solid tumors need additional blood supply for rapid growth, and they obtain this by rapid growth of new blood vessels, which is of course done using endothelial cells, so that the cancer can be said to be derived from such cells. Is that what the claim intends, i.e. solid tumors generally? Or do applicants intend just things like endothelioma? More precisely language is needed. Whatever choice is selected must be supported by the specification.

Specification

The parentage is confused:

A. The specification as filed has a blank in the first line where the SN should be. There is a filing date given, but no application has such a filing date.

B. The preliminary amendment says to add as a new first line that this is a CIP of 09/230829, filed 8/30/1999, but the same paper also says that this case is actually a CON of 09/241224.

C. The specification wording of "which claims priority to" is not proper. It must be more specific.

Applicants must replace this material with a clean and accurate statement of parentage.

This case lacks a proper abstract; the one provided is too brief as to structure of the compounds.

The scheme on page 28 is defective. The three steps must recite a reagent used, not a bare moiety. The same problem occurs on page 46. Applicants may wish to consider changes which were made in 08/692012 as well, e.g. for the "serinol" on page 64, which is not a moiety at all.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

January 3, 2002